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Received May 2, 1977

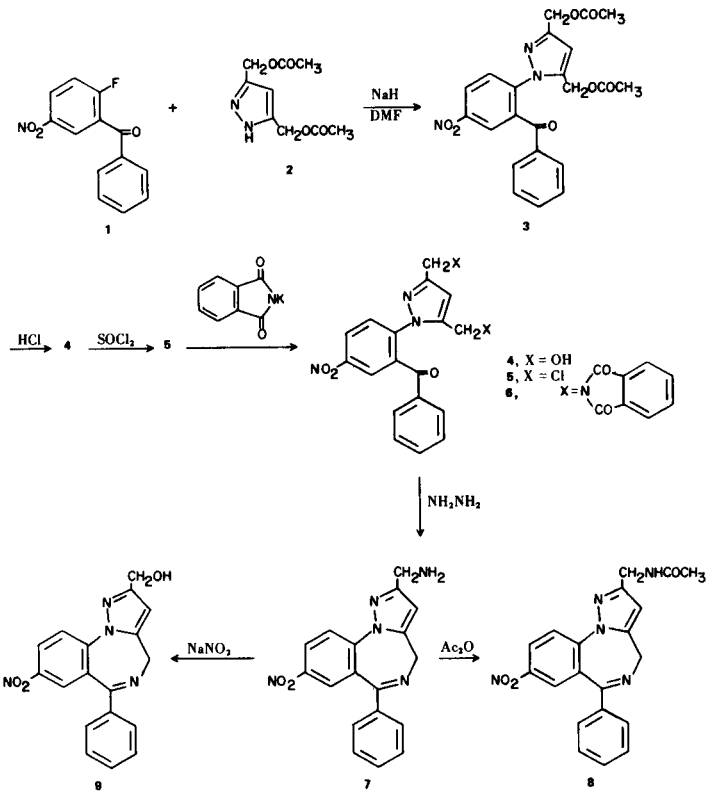
The preparation of 8-nitro substituted pyrazolobenzodiazepines from 2-fluoro-5-nitrobenzophenone (**1**) and 3,5-diacetoxymethylpyrazole (**2**) is reported.

J. Heterocyclic Chem., **14**, 1171 (1977)

The preceding paper in this series (1) discussed the synthesis of various 8-chloro-pyrazolo[1,5-*a*][1,4]benzodiazepines, starting from 2-fluoro-5-nitrobenzophenone (**1**). This same intermediate has now been used as the starting material for the synthesis of 8-nitropyrazolo [1,5-*a*][1,4]benzodiazepines.

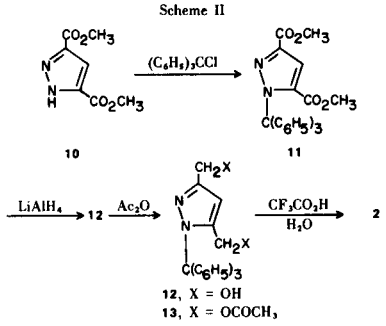
The nucleophilic displacement of fluorine in **1** by the sodium salt of 3,5-bis(acetoxymethyl)pyrazole (**2**) led to the crude noncrystalline benzophenone **3**. Without further purification, the acetoxy groups were removed by acidic hydrolysis to yield the diol **4**. Treatment of **4** with thionyl chloride gave the dichloro compound **5**, which upon treatment with potassium phthalimide in dimethylformamide yielded the bis-phthalimidobenzophenone **6**. To complete the synthesis of the pyrazolobenzodiazepine **7**, the phthalimido groups were moved by hydrazinolysis. Compound **7** was then either acetylated with acetic anhydride or diazotized with sodium nitrite to yield either compound **8** or compound **9**, respectively (Scheme I).

Scheme I



The other starting material used in this synthesis, the diacetoxypyrazole **2**, was prepared from 3,5-pyrazoledicarboxylic acid, dimethyl ester (**10**) (2) by protection of the ring with a trityl blocking group followed by reduction of the ester functions with lithium aluminum hydride. The resulting diol **12** was acetylated and the trityl group removed by treatment with aqueous trifluoroacetic acid to give the requisite pyrazole (Scheme II).

Scheme II



EXPERIMENTAL

Melting points were measured with a Thomas-Hoover capillary apparatus and are corrected. The ir spectra were recorded on a Digilab FTS14 or a Perkin-Elmer 621 spectrometer and nmr spectra on a Jeolco C-60H, a Varian XL-100 or HA-100 instrument using tetramethylsilane as an internal standard. Silica gel 60 (Merck, 60-230 mesh) was used for chromatography and either anhydrous sodium sulfate or magnesium sulfate was used for drying organic solutions.

3,5-Bis(acetoxymethyl)pyrazole (2)

To a solution of 90 ml. of trifluoroacetic acid and 15 ml. of water, cooled to -20° was added, in portions, 10 g. (0.022 mole) of **13**. After the addition was complete, the solution was stirred at -15° to -20° for 1 hour, poured into excess saturated potassium carbonate solution and extracted with ethyl acetate. The organic phase was dries, concentrated and the residue chromatographed on silica gel to give 4.7 g. (100%) of **2** as a pale yellow oil. The analytical sample was obtained as a colorless oil by bulb to bulb distillation, b.p. 175° (0.05 mm); ir (chloroform): 3440 (NH), and 1740 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.01 (6H, s, 2 CH_3), 5.10 (4H, s, 2 CH_2), 6.32 (1H, s, C=CH), and 11.86 (1H, s, NH).

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.66; H, 5.83; N, 13.24.

3,5-bis-(Acetoxymethyl)-2-(2-benzoyl-4-nitrophenyl)pyrazole (3).

A solution of 4.2 g. (20 mmoles) of **2** in 15 ml. of dimethyl-

formamide was added dropwise to a suspension of 960 mg. (20 mmoles) of sodium hydride (50% in mineral oil) in 25 ml. of dimethylformamide stirred at 0° and under argon. After the evolution of hydrogen had ceased, 4.9 g. (20 mmoles) of **1** was added in one portion. After stirring at 0° for 4 hours, the mixture was poured into ice-water and extracted with ethyl acetate. The organic phase was washed with diluted brine, dried and concentrated. The residue was chromatographed on silica gel using benzene/ethylacetate (1:1) as eluent. Removal of the solvents gave 7.1 g. (82%) of crude **3** as a gum which was not purified further. The nmr (deuteriochloroform) had signals at: δ 2.00 (3H, s, CH_3), †.07 (3H, s, CH_3), 4.82 (2H, s, CH_2), 5.10 (2H, s, CH_2) 6.33 (1H, s, C=CH), and 7.30-8.67 (8H, m, C_6H_5 + C_6H_3).

3,5-bis(Hydroxymethyl)-2-(2-benzoyl-4-nitrophenyl)pyrazole (**4**).

A solution of 5.6 g. (12.8 mmoles) of **3** in 100 ml. of 3*N* hydrochloric acid was refluxed for 3.5 hours. The solution was cooled, poured into excess saturated potassium carbonate and extracted with ethyl acetate. The organics were washed with brine, dried, concentrated and the residue chromatographed on silica gel with benzene/ethyl acetate (1:1) to give 3.35 g.(74%) of **4** as a pale yellow solid. An analytical sample was prepared by recrystallization from methanol-water, m.p. 145-147°; ir(potassium bromide): 3300 (broad OH), and 1680 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 4.10 (2H, d, CH_2), 4.50 (2H, d, CH_2), 4.87 (1H, t, OH), 5.57 (1H, t, OH), 6.12 (1H, s, C=CH), 7.40 (5H, s, C_6H_5) and 8.0-8.67 (3H, m, C_6H_3).

Anal. Calcd. for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.23; H, 4.14; N, 11.67.

3,5-bis(Chloromethyl)-2-(2-benzoyl-4-nitrophenyl)pyrazole (**5**).

A solution of 2 g. (5.7 mmoles) of **4** and 30 ml. of thionyl chloride was refluxed for 0.5 hours. The excess thionyl chloride was removed *in vacuo* and the residue partitioned with cold saturated potassium carbonate and ethyl acetate. The ethyl acetate extracts were washed with brine, dried and concentrated to give 2 g. (90%) of **5** as a tan solid. The analytical sample was obtained as tan plates by recrystallization from ethanol, m.p. 153-155°; ir (potassium bromide): 1675 cm^{-1} C=O); nmr (dimethyl sulfoxide-d_6): δ 4.35 (2H, s, CH_2), 4.95 (2H, s, CH_2), 6.43 (1H, s, C=CH), 7.48 (5H, bs, C_6H_5) and 8.03-8.77 (3H, m, C_6H_3).

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_3$: C, 55.40; H, 3.36; N, 10.77. Found: C, 55.11; H, 3.25; N, 10.50.

3,5-bis(Phthalimidomethyl)-2-(2-benzoyl-4-nitrophenyl)pyrazole (**6**).

A mixture of 12.8 g. (32.8 mmoles) of **5**, 18.5 g. (100 mmoles) of potassium phthalimide, and 250 ml. of dimethylformamide was stirred and heated at 65° for 18 hours. After cooling, the mixture was poured over ice, extracted with ethyl acetate, washed with diluted brine, dried and concentrated *in vacuo*. The residue was filtered through silica gel using ethyl acetate as an eluent. Removal of the solvent left 18.8 g. (94%) of **6** as a pale yellow solid, m.p. 220-224°. The analytical sample was prepared by recrystallization from acetone-hexane, pale yellow needles, m.p. 225-226.5°; ir (potassium bromide): 1780, 1720 and 1680 cm^{-1} (C=O).

Anal. Calcd. for $C_{34}H_{21}N_5O_7$: C, 66.75; H, 3.46; N, 11.45. Found: C, 66.55; H, 3.76; N, 11.37.

2-Aminomethyl-8-nitro-6-phenyl-4*H*-pyrazolo[1,5-*a*][1,4]benzodaizepine (**7**).

A solution of 7.2 g. (11.8 mmoles) of **6**, 4 g. of hydrazine hydrate, and 350 ml. of ethanol was refluxed for 5 hours. A precipitate of phthalhydrazide began forming after *ca.* 1 hour. The solution was cooled, concentrated and the residue triturated with ethyl acetate/methanol (4:1). The phthalhydrazide was removed by filtration and washed with the above solvent mixture. The filtrates were concentrated and the residue triturated with dichloromethane and filtered. Removal of the dichloromethane *in vacuo* left 3.8 g. (97%) of crude **7**, as a gum which was not purified further.

2-Acetamidomethyl-8-nitro-5-phenyl-4*H*-pyrazolo[1,5-*a*][1,4] benzodiazepine (**8**).

A mixture of 4 g. (12 mmoles) of **7**, 25 ml. of acetic anhydride and 5 ml. of triethylamine was stirred at room temperature for 1 hour. After pouring into ice water, the precipitate was collected by filtration and washed with water to give 3.5 g. (77%) of **8** as a yellow-tan solid, m.p. 208-211°. The analytical sample was obtained as tan plates by recrystallization from ethanol-water: m.p. 211-213°; ir (chloroform): 3450 (NH), and 1675 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.00 (3H, s, CH_3), 4.48 (2H, d, CH_2NH), 4.64 (2H, bs, CH_2) 6.32 (1H, s, C=CH), 6.45 (1H, bs, NH), 7.39 (5H, s, C_6H_5), and 8.08-8.48 (3H, m, C_6H_3).

Anal. Calcd. for $C_{20}H_{17}N_5O_3$: C, 63.99; H, 4.56; N, 18.65. Found: C, 63.80; H, 4.75; N, 18.48.

2-Hydroxymethyl-8-nitro-6-phenyl-4*H*-pyrazolo[1,5-*a*][1,4]benzodiazepine (**9**).

To a solution of 3.8 g. (11 mmoles) of **7** in 30 ml. of acetic acid and 5 ml. of water, was added dropwise a solution of 1.1 g. (16 mmoles) of sodium nitrite in 3 ml. of water. After stirring for 1 hour, the solution was warmed on a steam bath cooled and added to saturated potassium carbonate. The solid which was precipitated was filtered and chromatographed on silica gel using benzene-ethyl acetate (3:1) to elute 1.4 g. (24%) of the acetate of **9**. The acetate was non-crystalline and was characterized by nmr: δ 2.10 (3H, s, CH_3), 4.67 (2H, bs, CH_2), 5.20 (2H, s, CH_2O), 6.43 (1H, s, C=CH), 7.43 (5H, s, C_6H_5) and 8.10-8.53 (3H, m, C_6H_3). The desired alcohol was eluted from the column using benzene/ethylacetate (1:1) and was obtained in 27% yield. The analytical sample was obtained as faint yellow plates by recrystallization from methanol, m.p. 192-193.5°; ir (potassium bromide): 3341 cm^{-1} (OH); nmr (dimethylsulfoxide-d_6): δ 4.45 (2H, s, CH_2O); 4.65 (2H, bs, CH_2), 6.43 (1H, s, C=CH), 7.23 (5H, s, C_6H_5), 7.80-8.35 (3H, m, C_6H_3).

Anal. Calcd. for $C_{18}H_{14}N_4O_3$: C, 64.67; H, 4.22; N, 16.76. Found: C, 64.47; H, 4.40; N, 16.78.

1-Triphenylmethyl-3,5-pyrazoledicarboxylic Acid, Dimethyl Ester (**11**).

To a solution of 1.84 g. (10 mmoles) of **10** in 15 ml. of dimethylformamide, stirred at 0° under argon, was added 480 mg. (10 mmoles) of 50% sodium hydride (suspension in mineral oil). After the evolution of hydrogen had ceased, 2.7 g. (10 mmoles) of triphenylmethyl chloride in 20 ml. of dimethylformamide was added dropwise. The mixture was allowed to warm to room temperature, stirred 1.5 hours, poured into water and the resulting precipitate collected by filtration. After recrystallization from 2-ethoxyethanol-water, there was obtained 3.0 g. (70%) of **11**. The analytical sample was obtained as colorless needles by recrystallization from dimethylformamide-water, m.p. 212-213.5°; ir (potassium bromide) 1740 and 1720 cm^{-1} (2 C=O).

Anal. Calcd. for $C_{26}H_{12}N_2O_4$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.99; H, 5.30; N, 6.63.

1-Triphenylmethyl-3,5-dihydroxymethylpyrazole (**12**).

A solution of 25 g. (59 mmoles) of **11** in 800 ml. of tetrahydrofuran was added dropwsie to a slurry of 3.8 g. (100 mmoles) of lithium aluminum hydride in 400 ml. of tetrahydrofuran stirred at 0°. After warming to room temperature, the mixture was refluxed for 1 hour, cooled and the excess lithium aluminum

hydride decomposed by the dropwise addition of water, followed by 3*N* sodium hydroxide. The salts were filtered and washed with dichloromethane. The filtrates were concentrated to give 22 g. (100%) of **12** as a white solid, m.p. 180-182°. The analytical sample was obtained as colorless needles by recrystallization from methanol-water: m.p. 180-182°; ir (chloroform): 3600 cm^{-1} (OH), no carbonyl absorption; nmr (dimethylsulfoxide-d_6): δ 3.34 (2H, d, CH_2), 4.31 (2H, d, CH_2), 4.81 (1H, d, OH), 4.89 (1H, d, OH), 6.39 (1H, s, C=CH), 6.96-7.38 (15H, m, 3 C_6H_5).

Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.84; H, 6.11; N, 7.41.

1-Triphenylmethyl-3,5-diacetoxymethylpyrazole (**13**).

A solution of 19.5 g. (0.053 mole) of **12**, 90 ml. of acetic anhydride and 20 ml. of triethylamine was stirred at room temperature for 2.5 hours. After pouring into 1*N* sodium hydroxide, the solution was extracted with dichloromethane. The organic phase was dried, concentrated and the residue recrystallized from methanol to give 17.7 g. (73%) of **13**. The analytical sample was prepared from the same solvent: colorless plates, m.p. 119-121°; ir (chloroform): 1730 cm^{-1} (C=O); nmr (dimethylsulfoxide-d_6): δ 1.77 (3H, s, CH_3), 1.99 (3H, s, CH_3), 4.14 (2H, s, CH_2), 4.95 (2H, s, CH_2), 6.53 (1H, s, C=H), and 6.90-7.47 (15H, m, 3 C_6H_5).

Anal. Calcd. for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.06; H, 5.83; N, 6.13.

Acknowledgment.

The authors are grateful to Mr. G. Walsh for Technical Assistance. We also wish to thank the following members of our Physical Chemistry Department under the direction of Dr. R. Scott: Mr. S. Traiman for ir spectra, Dr. T. Williams for nmr spectra and Dr. F. Scheidl for nicroanalyses.

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